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10/756,825	01/13/2004	Yi Lu	ILL05-041-US	3704

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	**PAPER NUMBER**
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/756,825	LU ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,17-22 and 42-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,17-22 and 42-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/24/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

1. Examiner acknowledges the amendment filed on October 3, 2007. Applicant has amended claims 1, 17-22, 42-43, 50-51, 54-58, 60-63, 70-71; and cancelled claims 6-16, 23-41. Consequently claims 1-5, 17-22, 42-71 are currently pending and will be examined in this action.

Response to Arguments

2. Applicant's arguments filed October 3, 2007 have been fully considered but they are not persuasive. The claims that are being prosecuted are directed to product namely a sensor. Applicant has added limitations to independent claims 1, 17 and 57 that do not provide structural limitation. The limitation describes how the claimed sensor functions but does not result in a different product that is novel over the teachings of prior art.

Prior art teaches all the elements recited in steps a) through d) of independent claims 1, 17 and 57. The details provided by Applicant describe the conditions (heating /cooling temp) under which the desired results are obtained. These conditions would be relevant if a method was being prosecuted. However these conditions do not do not provide any patentable weight to the product claims.

Examiner would like to emphasize, the claimed size ranges of particles 35 nm used in the sensors of instant claims is also taught by prior art (Mirkin et al.).

Thus since all the elements of the sensors are taught by prior art, by routine optimization one of ordinary skill would have figured out that sensitivity of

these sensors can be increased further if particles of only 35 nm diameter are used.

Thus, an ordinary practitioner would have recognized that the results optimizable variables of time, temperature and size of particles could be adjusted to maximize the desired results. As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific sizes of the claimed particles was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Applicant argues that prior art cited is silent as regards to the use of particles and that Mirkin et al. do not recognize how assays can be improved by using bigger particle size. Examiner would like to point out that a sensor comprising particles of 35 nm will inherently have the properties recited with regard to rate of aggregation and rate of color change irrespective of the fact whether they were recognized as such by prior art or not.

Thus prior art cited is still valid and the 103 rejections are being maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1, 17 and 57 are being considered together. Since claims 17 and 57 are species of generic claim 1. With regards to all these claims, as indicated above under response to arguments the newly added limitation "a mixture of (a) the nucleic acid enzyme, (b) the substrates, (c) the first set of particles, and (d) the second set of particles, will form aggregates of the first and second set of particles, and formation of the aggregates will be at least 95% complete 10 minutes after the mixing." Is not being considered further since this describes

how the claimed sensor functions and does not provide any structural limitation to the claimed sensor.

6. Claims 1-5, 17-22, 42-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuenoud and Szostak (1995) Nature vol. 375: pp 611-614 in view of Mirkin et al. (US Pat. 6,361,944 issued Mar. 26, 2002); Frauendorf and Jaeschke (2000) Bioorganic & Medicinal Chemistry 9: 2521-2524 and further in view of Joyce and Breaker (1998) WO 98/49346 and Li and Lu (2000) J. of the American Chem. Soc., Wash. DC US vol. 122 no. 42 pp 10466-10467.

Regarding claims 1, 17 and 57 Cuenoud and Szostak teaches:

(a) a nucleic acid enzyme (see page 613 fig. 3b and fig. legend where DNA metalloenzyme is taught), comprising a cofactor binding site (Zn2+ and Cu2+ are taught as cofactors necessary for this enzyme to function hence the enzyme inherently must have a cofactor binding site);

(b) substrates for the nucleic acid enzyme, comprising first polynucleotides (see page 613 fig. 3b where substrate polynucleotide S1 and S2 are taught);

(c) Cuenoud and Szostak teach a second polynucleotides (S1 described above) ; and

(d) a third polynucleotides (S2 described above);

wherein the first polynucleotides comprise or are at least partially complementary to the second polynucleotides (see fig 1 b where catalyst—3' end of polynucleotide comprising enzyme is partially complementary to the second polynucleotides S1), and

the first polynucleotides comprise or are at least partially complementary to the third polynucleotides (see fig 1 b where catalyst—5' end of polynucleotide comprising enzyme is partially complementary to the third polynucleotides S2).

Regarding claims 1, 17 and 57 Cuenoud and Szostak do not teach:

a) A sensor system for detecting an effector or cofactor, and optionally an effector binding site

(c) a first set of particles, wherein the polynucleotides are attached to the particles at the 3' terminus; and

(d) a second set of particles, wherein the polynucleotides are attached to the particles at the 5' terminus.

Regarding claims 5, 22, 62, Cuenoud and Szostak teach Zn2+ and Cu2+ (see above).

Regarding claims 1, 17 and 57 Mirkin et al. teach

(c) a first set of particles comprising second polynucleotides, wherein polynucleotides are attached to the particles at the 3' terminus(See Fig 16 B oligo labeled 2 wherein polynucleotides are attached to the particles at the 3' terminus through the thiol bond shown by S; and

(d) a second set of particles comprising third polynucleotides, wherein the polynucleotides are attached to the particles at the 5' terminus (See Fig 16 B oligo labeled 1 wherein polynucleotides are attached to the particles at the 3' terminus through the thiol bond shown by S);

wherein the first polynucleotides comprise or are at least partially complementary to the second polynucleotides, and the first polynucleotides comprise or are at least partially complementary the third polynucleotides (See Fig. 16 B where the 3' half of first polynucleotide top strand is complementary to second polynucleotides, wherein polynucleotides are attached to the particles at the 3' terminus through the thiol bond shown by S. The 5' half of first polynucleotide top strand is complementary to second polynucleotides, wherein polynucleotides are attached to the particles at the 5' terminus through the thiol bond shown by S. Also see col. 16 lines 29-40 where nanoparticles that can be linked to these the second and third polynucleotides of the invention are described. Also see Fig. 17 A-E and col. 15, lines 7-15).

Regarding claims 3, 20, 60 Mirkin et al. teaches wherein the first set of particles and the second set of particles comprise gold (see col. 16, lines 29-31 where gold nanoparticles are taught).

Regarding claims 4, 21, 61 Mirkin et al. teaches wherein the first set of particles and the second set of particles comprise a material selected from the group consisting of metals, semiconductors and latex (see col. 16 lines 31-32 where metal and semiconductors are taught. See col. 6 line 53 where latex is taught).

Regarding claims 17, 42, and 57 Mirkin et al. further teaches the set of particles have an average diameter of at least 30 nm. (see col. 16 lines 37-40 where size range from about 5 to about 50 nm is taught thereby average diameter of at least 30 nm is taught by Mirkin et al.).

Regarding claims 18, 43, 58 Mirkin et al. teaches wherein the second set of particles have an average diameter of at least 35 nm (see col. 16 lines 37-40 where size range from about 5 to about 50 nm is taught thereby an average diameter of at least 35 nm is taught by Mirkin et al.).

Regarding claim 50, Mirkin et al. teaches wherein the second polynucleotides are attached to the particles at the 3' terminus and the third polynucleotides are attached to the particles at the 5' terminus. (See Fig 16 B oligo labeled 1 wherein polynucleotides are attached to the particles at the 3' terminus through the thiol bond shown by S; and

(d) a second set of particles comprising third polynucleotides, wherein the polynucleotides are attached to the particles at the 5' terminus (See Fig 16 B oligo labeled 2 wherein polynucleotides are attached to the particles at the 3' terminus through the thiol bond shown by S);

Regarding claims 1, 17 and 57 Frauendorf and Jaeschke teach

a) A sensor system for detecting an effector or cofactor (see page 2521 where sensor is taught for detection of theophylline (effector) in a concentration dependent manner using an allosteric nucleozyme (see abstract).

Regarding claims 44, 51 & 63, Frauendorf and Jaeschke teach sensor further comprising a buffer (see page 2523 par. 10 where HEPES buffer is taught).

Regarding claims 45-46, 52-53 & 64-65, Frauendorf and Jaeschke teach wherein the buffer is selected to have a pH of 6.2 to 10.2 (claims 45, 52, 64) and pH range of 7.2 to 9.0 (claims 46, 53 and 65) (see Frauendorf and Jaeschke

page 2523 par. 10 where HEPES buffer at pH 7.6 is taught and par. 11 where Tris buffer at pH 7.6 is taught. Thus by teaching two different buffers with pH within the claimed range Frauendorf and Jaeschke teach buffers encompassing pH range of pH 6.2 to 10.2 (claims 45, 52, 64) and 7.2 to 9.0 (claims 46, 53 & 65)).

Regarding claims 47, 54 & 66, Frauendorf and Jaeschke teach wherein components of the sensor system are in an aqueous solution having an ionic strength of at least 0.20 (see page 2523 par. 10 where buffer containing 200 mM KCl = 0.2 M KCl = ionic strength of at least 0.2 is taught).

Regarding claims 48, 55 & 67, Frauendorf and Jaeschke teach wherein the nucleic acid enzyme is present at a concentration of at least 0.2 μM (see page 2523 par. 10 where 1.72 μM of SWI58 nucleic acid enzyme is taught. Thereby teaching a sensor wherein the nucleic acid enzyme is present at a concentration of at least 0.2 μM).

Regarding claims 49, 56 & 68, Frauendorf and Jaeschke teach, wherein the first polynucleotides are present at a concentration of at least 1.5 nM (see page 2524 par. 1 where 1.14 μM = 1140 nM of SWI13DF (first polynucleotide) is taught. Thus Frauendorf and Jaeschke teach the first polynucleotides are present at a concentration of at least 1.5 nM).

Regarding claims 2, 19, 59 Joyce and Breaker teach wherein the nucleic acid enzyme comprises DNA (see title).

Regarding claims 69, 70 and 71 Joyce and Breaker teach heavy metal ion Pb^{+2} (see Joyce and Breaker see page 40 line 12).

It would be prima facie obvious to one of ordinary skill in the art to use the nano particles of Mirkin et al. in the system taught by Cuenoud and Szostak to produce a sensor that can detect an effector in concentration dependent manner at the time of the invention.

The motivation to do so is provided to one of ordinary skill by teachings of Mirkin et al., Frauendorf and Jaeschke, Joyce and Breaker and Li & Lu.

Mirkin et al. teach detection of nucleic acids using a colorimetric assay utilizing gold particles. Mirkin et al. state " Presently preferred for use in detecting nucleic acids are gold nanoparticles. Gold colloidal particles have high extinction coefficients for both the bands that give rise to their beautiful colors. These intense colors change with size, concentration, interparticle distance, and extent of aggregation and shape (geometry) of the aggregates, making these materials particularly attractive for colorimetric assays" (see col. 16, lines 64-col. 17 lines 1-4). They also show using these gold particles as low as 3 femtomole of target could be detected colorimetrically (see col. 59 line 15-16).

Teaching of Frauendorf and Jaeschke make it clear for one of ordinary skill that a nucleic acid based sensor system can be used for detecting different types of analytes. Frauendorf and Jaeschke state "The combination of allosteric ribozymes with -----should in principle allow the construction of detection systems for a wide variety of analytes, ranging from metal ions over amino acids, antibiotics to proteins and even whole cells" (see Frauendorf and Jaeschke page 2523 par. 7). Frauendorf and Jaeschke teach detection of analytes (effectors) in

concentration dependent manner is possible using the nucleic acid enzyme system.

Joyce and Breaker teach a DNA enzyme capable of functioning efficiently in presence of divalent heavy metal cation Pb^{2+} (Joyce and Breaker see page 40 line 12). One of ordinary skill in the art recognizes the utility of being able to detect heavy metal ions such as Pb^{2+} that are extremely toxic to human and cause lead poisoning. In this context Li and Lu state " Lead is a common environmental contaminant. Low-level lead can lead to a number of adverse health effects. The lead level in the blood is considered toxic when it is greater than or equal to 480nM. Current methods for lead detection, such as------often require sophisticated equipment or sample treatment. Simple inexpensive methods that permit real-time sampling of Pb^{+2} are important in the fields of environmental monitoring, clinical toxicology, wastewater treatment, and industrial process monitoring" (see page 10466 par. 2).

Hence one of ordinary skill in the art would be motivated to build gold particles based nucleic acid sensors to detect heavy metal such as Pb^{2+} contamination of water or other environmental samples. Such a sensor would have the sensitivity and advantages of the colorimetric as pointed out above by Mirkin et al. and would permit real-time sampling of Pb^{+2} are important in the fields of environmental monitoring, clinical toxicology, wastewater treatment, and industrial process monitoring.

Conclusion

7. All claims under consideration 1-5, 17-22 and 42-71 are being rejected over prior art.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

/Teresa Strzelecka/

Teresa Strzelecka

Primary examiner, Art Unit 1637

October 17, 2007